Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 U.S. Case-Control Studies. VI. Nonepithelial Cancers among Adults

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Nonepithelial ovarian cancers are rare, and little is known about their etiology. Of particular interest are the effects of oral contraceptive use and pregnancy, both of which are associated with large decreases in risk for epithelial ovarian cancer. We examined the risk factors for nonepithelial ovarian tumors by combining data from four case-control studies conducted in the United States. We compared personal characteristics of 38 germ cell cases and 45 stromal cases, respectively, with 1,142 and 2,617 general population controls. All subjects were over age 18 years. For germ cell tumors, there was a weak negative association with parity but no consistent pattern of decreasing risk with increasing parity. In contrast, relative to nulligravid women, gravid nulliparous women were at increased risk of developing a germ cell cancer [odds ratio (OR) = 4.8, 95% confidence interval (CI) = 1.2–18.6]. The use of oral contraceptives was also associated with elevated risk (OR = 2.0, 95% CI = 0.77–5.1); however, no clear trends in risk were observed. For stromal tumors, oral contraceptive use was associated with decreased risk (OR = 0.37, 95% CI = 0.16–0.83), whereas pregnancy was associated with a small elevation in risk. A trend of increasing risk with increasing age at first term pregnancy was observed, with an odds ratio of 3.6 (95% CI = 1.0–12.5) for a first birth after age 29 years. Risk factors for nonepithelial ovarian cancers do not appear to parallel each other or those for epithelial ovarian cancer. (Epidemiology 1992;3:490–495)

Keywords: nonepithelial ovarian neoplasms, germ cell neoplasms, sex cord-stromal neoplasms, pregnancy, oral contraceptives, parity, adults.

Nonepithelial ovarian cancers are rare, accounting for less than 7% of all malignant ovarian tumors. Germ cell and sex cord-stromal tumors constitute the majority of these neoplasms. In this paper, we will refer to sex cord-stromal tumors simply as stromal tumors for ease of presentation. Age-standardized incidence rates for malignant germ cell and stromal tumors are 3.7 ± 0.3 and 2.1 ± 0.2 per million women per year, respectively (Surveillance, Epidemiology, and End Results Program, unpublished data). Germ cells originate from the yolk sac endoderm and migrate to the ovary during early embryonal life.[1] Germ cell tumors constitute

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approximately 20% of benign ovarian tumors but less than 3% of ovarian malignancies. Malignant germ cell tumors occur predominantly in girls and young women, with the peak incidence occurring among those age 15–19 years. Teratomas and dysgerminomas, which are cytologically similar to seminomas of the testis, constitute the majority of germ cell tumors. Only one case-control study has addressed risk factors for malignant germ cell ovarian tumors.[2] These authors examined *in utero* exposures and found increased risks associated with maternal use of hormones during the first trimester of pregnancy, high prepregnancy body mass, and young maternal age.

Both the epithelial and stromal cells of the ovary arise from the mesoderm; epithelial cells arise from the celomic epithelium, and stromal cells arise from the adjacent mesenchyma of the medulla.[1,3] As with germ cell tumors, stromal tumors account for a larger proportion of benign ovarian tumors (12%) than of malignant tumors (2%). Like epithelial ovarian cancers, stromal cancers occur with increasing frequency in older women. The most common malignant stromal tumors arise from the granulosa cells, which are involved in the synthesis of estrone and the formation of the corpus luteum.[1,3] No etiologic study of these tumors has been conducted. Similarities between stromal and epithelial ovarian cancers in age-specific incidence, however, prompted us to investigate exposures influencing epithelial ovarian cancer risk (for example, pregnancy and oral contraceptive use) for possible associations with the risk of stromal ovarian cancer.

Subjects and Methods

This report is part of a collaborative analysis that combined epidemiologic data on ovarian cancer from 12 case-control studies conducted in the United States.[4] Studies included in the collaborative analysis satisfied the following criteria: the study must have included women newly diagnosed with ovarian cancer at a U.S. hospital; control women must have resided in the United States during the period of case ascertainment and could not have been selected on the basis of gynecologic conditions; characteristics of study subjects must have been ascertained through personal interviews using structured questionnaires; and questionnaire data must have been coded and stored electronically. Four of the 12 studies collected information from women with nonepithelial ovarian cancer. Table 1 lists these four studies along with the number of women with germ cell and stromal cancers and control women included in each analysis. All four of these studies selected controls from the general population. Control women who had or might have had a bilateral oophorectomy were excluded. Further information concerning individual study protocols can be found in the paper by Whittemore *et al*[4] and in the publications listed in Table 1.[5–8] Table 2 compares the age and histologic subtype distributions of study cases with cases identified by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, which records all resident cases diagnosed in nine geographic populations across the United States. Owing to the age restrictions of the respective studies, women with germ cell tumors included in this analysis

TABLE 1. Case-Control Studies Including Women with Nonepithelial Ovarian Cancer

Study	Age Group	Cases				Controls			Reference
		Germ Cell	Sex-Cord Stromal	Diagnosis: Year	Diagnosis: Place	No.*	No.†	Source	
1	18–80	6	7	1978–1981	Boston	43	117	Town directories	5
2	20–79	3	5	1977–1980	New York State	45	260	Motor vehicle files	6
3	50–74	2	16	1975–1979	Seattle and Utah	169	663	RDD‡ and household phone surveys	7
4	20–54	27	17	1980–1982	6 SEER areas§	885	1,577	RDD phone surveys	8
Total		38	45			1,142	2,617		

* Number included in analysis of germ cell tumors.
† Number included in analysis of sex cord-stromal tumors.
‡ Random-digit-dial.
§ Atlanta, Connecticut, Detroit, Iowa, San Francisco-Oakland, Seattle.

TABLE 2. Histologic and Age Distribution of Study Cases and SEER Cases*

	Study Cases		SEER Cases	
	Number	%	Number	%
Germ cell				
Histology				
Dysgerminoma	13	34	70	32
Endodermal sinus	4	10	35	16
Embryonal	0	0	11	5
Teratoma	20	53	97	45
Other	1	3	4	2
Age at diagnosis				
≤19	0	0	68	31
20-34	30	79	99	46
≥35	8	21	50	23
Sex cord-stromal				
Histology				
Granulosa-stromal cell	36	80	140	91
Androblastoma	4	9	7	5
Gynandroblastoma	1	2	1	1
Unclassified	4	9	5	3
Age at diagnosis				
≤19	0	0	5	3
20-44	13	29	32	21
45-59	25	55	60	39
≥60	7	15	56	37

* SEER cases include women diagnosed between 1977 and 1981 in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle, and Utah.

tended to be older than those from the SEER registry, while the reverse was true of women with stromal tumors.

We computed odds ratios (OR) and 95% confidence intervals (CI) from a conditional logistic regression,[9] stratified jointly by study and 5-year age group. Studies 3 and 4 were further stratified by their constituent study centers.[7,8] All regressions were performed on EGRET software[10] and include year of birth as a continuous variable to control for any case-control differences in year of interview that might bias comparison of temporal variables such as oral contraceptive use. Not all studies provided data for all variables relevant to a given topic. Thus, different regressions use data from different studies. Furthermore, women with unknown values of a variable were deleted from regressions containing that variable. Thus, total case and control numbers vary within Tables 3 and 4.

Results

Germ Cell Tumors

Data on *in utero* exposures were not collected by the four studies analyzed here. Table 3 presents the associations between selected adolescent and early adulthood exposures and the development of a germ cell ovarian cancer among women diagnosed with this type of tumor in their twenties or later. Parity was associated with a small decrease in risk of developing a germ cell cancer (OR = 0.71, CI = 0.33-1.5), but no trend of decreasing risk with increasing number of births was observed. Among ever-married nulliparous women, incomplete pregnancies (that is, miscarriages and abortions) were associated with increased risk (OR = 4.8, CI = 1.2-18.6, adjusting for oral contraceptive use). None of the women developing germ cell cancers reported an ectopic pregnancy or a stillbirth. Based on the occurrence of these events among controls and adjusting for age, however, only 0.6 ectopic pregnancies and 1.2 stillbirths might have been expected among the cases. Age at menarche, age at first term pregnancy, and duration of lactation were not associated to any appreciable degree with the development of a germ cell ovarian cancer.

A history of ever having used oral contraceptives was associated with elevated risk of developing a germ cell tumor, but the confidence interval was wide (OR = 2.0, CI = 0.77-5.1). There were no clear trends in risk with duration of use or recentness of use.

Risk was elevated among women who were overweight as teenagers (OR = 2.8, CI = 0.75-10.3, for body mass index >28 *vs* ≤ 28; data from Studies 2 and 4). No trend of increasing risk with increasing body mass index was observed, however. Adult obesity, measured as either usual adult body mass (Studies 3 and 4) or body mass at interview (Studies 2 and 3), was not associated with increased risk.

Data on alcohol consumption were available only from Study 4. In this study, however, cases were less likely to report drinking alcohol in the 5 years before interview than were controls (OR = 0.31, CI = 0.11-0.90, adjusting for education).

Information on the occurrence of cancer among a woman's first degree relatives was available from Studies 1 and 4. A family history of ovarian cancer was associated with elevated risk, but this estimate is based on only a few cases (OR = 3.4, CI = 0.61-19.5).

Sex Cord-Stromal Tumors

Table 4 presents associations between selected factors and the development of stromal ovarian cancers. Term pregnancies were associated with a slight increase in risk (OR = 1.6, CI = 0.57-4.3), but no trend in risk with increasing number of pregnancies was observed. Among ever-married nulliparous women, incomplete pregnancies were associated with an elevation in risk (OR = 9.2, CI = 0.77-110.1), but this estimate is unstable owing to the small number of nulliparous cases. Stillbirths were also associated with some eleva-

TABLE 3. Germ Cell Ovarian Cancer Risk According to Selected Factors

	Cases		Controls			
	Number	%	Number	%	OR*	95% CI
Term pregnancies†						
0	16	42	229	20	1.0	
≥1	22	58	912	80	0.71	0.33-1.5
1	5	13	170	15	0.57	0.20-1.7
2-3	11	29	548	48	0.68	0.27-1.7
≥4	6	16	194	17	2.3	0.63-8.1
Oral contraceptive use‡						
None	7	18	358	31	1.0	
Any	31	82	784	69	2.0	0.77-5.1
≤2 years of use	13	34	288	25	2.3	0.81-6.4
3-4 years of use	7	18	155	14	1.7	0.53-5.5
≥5 years of use	11	29	326	28	1.9	0.65-5.7
≤2 years since last use	15	39	155	14	2.6	0.92-7.5
3-5 years since last use	6	16	146	13	1.7	0.49-5.6
≥6 years since last use	9	24	415	36	1.5	0.47-4.7

* All odds ratios are adjusted for age, study, and year of birth.
† Defined as pregnancies of at least 20 weeks gestation. Adjusted for oral contraceptive use.
‡ Adjusted for parity.

tion in risk (OR = 2.7, CI = 0.79-9.1). No ectopic pregnancy was reported by women with stromal tumors, but only 0.5 such pregnancies would have been expected based on the age-adjusted occurrence of ectopic pregnancies among controls. Increasing age at first term birth was associated with increasing risk of developing a stromal cancer (8% increase in risk per year, CI = 1-15%, P_{trend} = 0.02), with a 3.6-fold increase in risk associated with a first birth occurring after age 29 years (CI = 1.0-12.5). No appreciable change in risk was associated with duration of lactation, age at menarche, age at menopause, type of menopause (natural *vs* artificial), history of hysterectomy, and history of tubal ligation.

A history of ever having used oral contraceptives was associated with decreased risk of developing a stromal cancer (OR = 0.37, CI = 0.16-0.83). There was a suggestion that increasing duration of use was associated with decreasing risk (11% decrease in risk per year of use, CI = 1%-23%, P_{trend} = 0.11). The protective association for oral contraceptives was observed most strongly among women who stopped using them 6 or more years before diagnosis (OR = 0.22, CI = 0.07-0.69).

The use of estrogen replacement therapy starting after age 40 years was associated with a drop in risk (OR = 0.43, CI = 0.15-1.2). One case (a nulligravid woman) and two controls (one nulligravid, the other multiparous) reported the use of fertility medications, yielding a substantial but unstable elevation in risk (OR = 13.4, CI = 0.94-190.7; data from Studies 1 and 2 only).

Some elevation in risk was observed for women who were overweight during their teenage years (OR = 3.6, CI = 0.72-15.6, for body mass index >28 *vs* ≤28), but we found no trend of increasing risk with increasing body mass. No clear association was seen for the effects of adult body mass.

None of the women with stromal tumors reported the diagnosis of ovarian cancer in a first degree relative. On the other hand, based on the occurrence of ovarian cancer in relatives of controls and adjusting for the age of the subject, only 0.2 cases would have been expected to have had a family history of ovarian cancer in a mother or sister.

Discussion

Combining data from several case-control studies provides an opportunity to examine the etiology of nonepithelial ovarian tumors. Although the combined numbers of patients are small, these analyses serve to generate hypotheses for future study. Limitations of this analysis include varying response rates in the individual studies, the possibility of confounding by unmeasured variables, and potential pitfalls in combining the studies. Although common definitions were used to recode all variables, the data nevertheless derive from questions whose wording varied across studies

TABLE 4. Sex Cord-Stromal Ovarian Cancer Risk According to Selected Factors

	Cases		Controls			
	Number	%	Number	%	OR*	95% CI
Term pregnancies†						
0	5	11	313	12	1.0	
≥1	40	89	2,301	88	1.6	0.57-4.3
1	7	15	275	10	2.0	0.62-6.6
2-3	20	44	1,251	48	1.4	0.48-3.9
≥4	13	29	775	30	1.6	0.52-5.2
Age at first birth‡						
<20 years	6	15	482	21	1.0	
20-24 years	16	40	1,051	46	1.5	0.55-4.2
25-29 years	11	27	560	24	2.3	0.77-7.0
≥30 years	7	17	190	8	3.6	1.0-12.5
Oral contraceptive use§						
None	34	75	1,506	57	1.0	
Any	11	24	1,106	42	0.37	0.16-0.83
≤2 years of use	3	7	483	18	0.27	0.08-0.95
3-4 years of use	4	9	159	6	0.85	0.26-2.8
≥5 years of use	4	9	441	17	0.35	0.11-1.1
≤2 years since last use	3	7	126	5	0.74	0.19-2.9
3-5 years since last use	3	7	140	6	0.61	0.16-2.2
≥6 years since last use	4	9	708	31	0.22	0.07-0.69

* All odds ratios are adjusted for age, study, and year of birth.
† Defined as pregnancies of at least 20 weeks gestation. Adjusted for oral contraceptive use.
‡ Adjusted for parity and oral contraceptive use.
§ Adjusted for parity.

and could thus have elicited different responses, thus compounding measurement error. In addition, because the studies did not include girls and elderly women, the results may not apply to the extremes of age. Finally, no independent histologic review was undertaken as part of this collaborative analysis. Nevertheless, slide reviews using the World Health Organization histologic classification scheme[11] were undertaken as part of Studies 1, 2, and 4. In addition, excellent agreement has been demonstrated between histologic diagnoses made by hospital pathologists and by an expert panel of gynecologic pathologists for both germ cell and stromal ovarian tumors.[12]

The study by Walker *et al*[2] addressed only *in utero* exposures in patients under age 35 years. They found that mothers of children with germ cell ovarian cancers were more likely to be young at the birth of the index child, to have been exposed to hormonal drugs during the first trimester of that pregnancy, and to have been overweight before that pregnancy. None of these prenatal exposures has been associated with increased risk of benign ovarian teratomas.[13] Data on prenatal exposures were not available in the studies analyzed here. Instead, we examined correlates of hormonal exposures during puberty and early adulthood, which may also influence cancer development among the age group under study.

The data suggest that, relative to nulligravid women, gravid nulliparous women are at increased risk of developing a malignant germ cell ovarian tumor. This finding raises the possibility that some aspect of a woman's inability to carry to term, as opposed to her inability to conceive, may play a role in the development of a germ cell ovarian tumor.

In an earlier analysis of data from Study 4, a small elevation in risk of germ cell tumors among short-term oral contraceptive users was observed[8]; a similar elevation in risk was seen in this combined analysis. Risk was elevated, however, among users of all durations, suggesting that perhaps users and nonusers differ on some other variable that correlates with oral contraceptive use. Further studies of germ cell ovarian cancers should include an assessment of both *in utero* exposures and exposures occurring during puberty and a woman's reproductive years.

The etiology of stromal ovarian tumors has not been previously addressed. The age distribution of this nonepithelial ovarian cancer is similar to that of epithelial

ovarian tumors. High parity and the use of oral contraceptives have been shown to reduce the risk of epithelial ovarian cancer.[14,15] Both are associated with similar biological sequelae (that is, the cessation of ovulation and the suppression of pituitary gonadotropins). Cramer and Welch[16] hypothesized that risk factors for epithelial and stromal tumors will be similar, except for those factors that may predispose to inclusion cyst formation.

Consistent with a previous report,[8] this analysis found reduced risk of stromal ovarian cancer associated with oral contraceptive use; decreasing risk was associated with increasing length of use. Also, consistent with the associations for epithelial tumors,[14] the strongest negative associations were observed among women who last used oral contraceptives in the more distant past. This finding suggests that the older high-potency contraceptive formulations may have conferred greater protection against malignancy.

In contrast, parity, incomplete pregnancies, and stillbirths all were associated with elevations in risk. In addition, the risk of developing a stromal ovarian cancer increased with increasing age at first term pregnancy. The detrimental association between pregnancy and risk of developing a stromal tumor contrasts with its apparent protection against epithelial ovarian tumors.

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